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CRITICAL REVIEW

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Current commercialization status of electrowetting-on-dielectric (EWOD) digital microfluidics

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The emergence of electrowetting-on-dielectric (EWOD) in the early 2000s made the once-obscure electrowetting phenomenon practical and led to numerous activities over the last two decades. As an eloquent microscale liquid handling technology that gave birth to digital microfluidics, EWOD has served as the basis for many commercial products over two major application areas: optical, such as liquid lenses and reflective displays, and biomedical, such as DNA library preparation and molecular diagnostics. A number of research or start-up companies (*e.g.*, Phillips Research, Varioptic, Liquavista, and Advanced Liquid Logic) led the early commercialization efforts and eventually attracted major companies from various industry sectors (*e.g.*, Corning, Amazon, and Illumina). Although not all of the pioneering products became an instant success, the persistent growth of liquid lenses and the recent FDA approvals of biomedical analyzers proved that EWOD is a powerful tool that deserves a wider recognition and more aggressive exploration. This review presents the history around major EWOD products that hit the market to show their winding paths to commercialization and summarizes the current state of product development to peek into the future. In providing the readers with a big picture of commercializing EWOD and digital microfluidics technology, our goal is to inspire further research exploration and new entrepreneurial adventures.

Introduction

While microfluidics as a technology is in general considered mature with the global microfluidics market estimated at \$8.7B for products (including \$3.8B for devices) in 2018,[1] droplet and digital microfluidics are viewed as relatively new and niche sectors. This review deals with digital microfluidics, shown in Fig. 1, starting with electrowetting as the underlying mechanism.

Akin to electrocapillarity by Lippmann,[7] electrowetting makes a liquid appear to wet a surface more than the inherent ability when applied of an electric field. However, conventional electrowetting, first described in 1981 for a liquid electrolyte on a metal by Beni and Hackwood,[8] was not significant enough (*e.g.*, contact angle change was not large enough) for engineering applications. The electrowetting effect was found significant in around 1993 by the University of Joseph Fourier when a dielectric layer added onto the metal surface allowed application of high voltages.[9] Coined as electrowetting-on-dielectric (EWOD)[2,10,11] to differentiate it from conventional electrowetting[8] and continuous electrowetting,[12,13] EWOD was shown to be capable of not only switching a droplet between beading and wetting[9] (Fig. 2(a)) but also moving it along desired paths on a surface (Fig. 2(b)) by Nanolytics, UCLA, and Duke University in around 2000.[14–16] Later, EWOD was shown to generate water droplets from an on-chip reservoir as well as move, split, and merge them, establishing the four essential

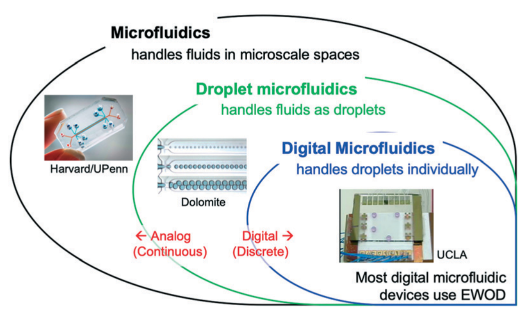

Fig. 1 As a subset of microfluidics, droplet microfluidics handles fluids as discrete entities, *e.g.*, droplets. As a further subset, digital microfluidics can manipulate individual droplets independently. One may relate digital microfluidics (or microfluidic circuits) to digital electronic circuits and continuous flow microfluidics to analog circuits.[2,3] Images adapted from ref. 4 with permission from Springer Nature, copyright 2013, from ref. 5 with permission from Dolomite Microfluidics, and from ref. 6.

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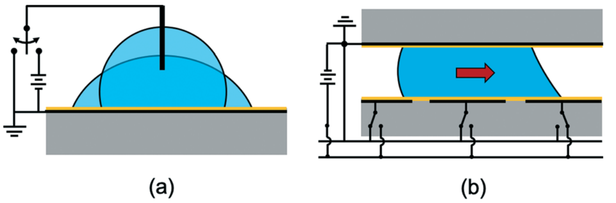

Fig. 2 Electrowetting effects shown on an EWOD surface. (a) A droplet beads on or wets a hydrophobic surface with voltage off or on, respectively. (b) A droplet wets a hydrophobic surface where voltage is applied and slides to that side.

microfluidic operations[17] in air (as well as in oil) and convincing the community that digital microfluidics and lab-on-a-chip applications would someday be possible. The field of electrowetting has taken off, as the growing number of publications in Fig. 3 indicates.

Realizing the promising utility of EWOD for applications, company activities began to emerge mainly for optical and biomedical applications while academic researchers continued exploring additional applications areas.[18–20] The field of electrowetting had a strong presence of companies even from the beginning: Varioptic,[21] Nanolytics,[14,16] and Philips Research.[22] In optical applications, Varioptic has pioneered a liquid lens and introduced a collection of products in the market, and Liquavista successfully prototyped a reflective display based on the video-speed display initiated by Philips Research.[22] In the biomedical field, Advanced Liquid Logic has developed a DNA sample preparation instrument, and GenMark Diagnostics and Baebies introduced diagnostic instruments to perform molecular assays, immunoassays and enzymatic assays in recent years.[23] These successes led to a flurry of acquisitions involving multinational companies (*e.g.*, Corning, Amazon, and Illumina) and attracted a slew of additional start-ups. While the strong commercialization activities helped define specific applications early on and address the well-known reliability problem of electrowetting devices, solutions to the problem were not disseminated promptly. For optical applications, EWOD devices would now survive millions of actuation cycles by optimizing the liquid materials and improving the dielectric materials and their depositions.[24]

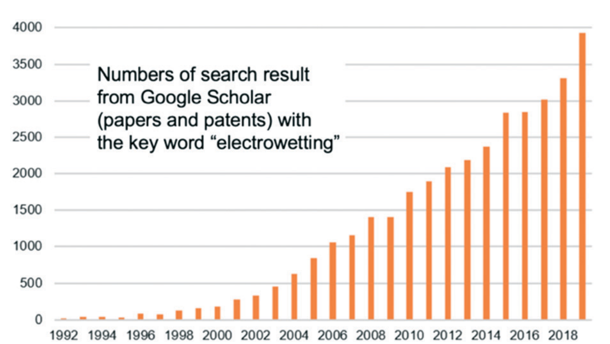

Fig. 3 The numbers of search counts in Google Scholar for the term "electrowetting" in papers and patents. Note the jump in early 2000s.

Although device reliability still remains as a major issue for biomedical applications, limiting the current products to handle nucleic acid solutions and prompting an opposite mechanism called electrodewetting to eliminate the main culprits (*e.g.*, hydrophobic coating),[25] the persisting success of liquid lenses and the recent FDA approvals of diagnostic instruments evidence that EWOD is a powerful and versatile technology with wide and far-reaching potential for the years to come.

In this review, we summarize the history behind the electrowetting products that hit the market and their paths to commercialization. The goal is to give readers a big picture of electrowetting in industry, providing a chance for academic researchers to appreciate the relevance of their work and encouraging potential entrepreneurs to explore new adventures.

The liquid lens

An aqueous droplet that beads on a hydrophobic surface can be switched to appear to be wetting the surface by applying an electric potential between the droplet and the substrate, as illustrated in Fig. 2(a). The University of Joseph Fourier (Grenoble, France) filed a patent for a variable focus lens consisting of a sessile drop in an immiscible liquid actuated by EWOD (Fig. 4(a)) in 1997,[21] and its inventor Bruno Berge founded Varioptic (Lyon, France) in 2002. Compared with conventional motorized lens, the liquid lens has many advantages: (i) no wear and silent operation, (ii) fast actuation (<50 ms), (iii) high mechanical shock resistance (>2000 g), and (iv) low power consumption (<20 mW with a driver).[26] In competition, Philips Research developed its liquid lens and demonstrated a camera in 2004.[27,28] In addition to controlling the focal length by EWOD, both companies developed additional functions such as variable

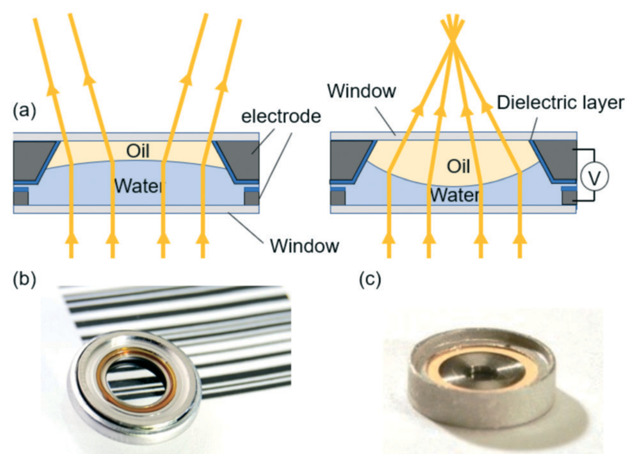

Fig. 4 Variable focus liquid lens. (a) Upon applying voltage, the water–oil meniscus changes its curvature, altering the focal length of the lens. (b) Varioptic's liquid lens assembly placed on a barcode, adapted from ref. 39 with permission from Corning Technology Center – Lyon. (c) Philips' liquid lens for camera phones, courtesy of S. Kuiper.

tilt and image stabilization and also found that optical aberration can be greatly reduced by adding a resistive layer between the insulation layers.[29,30] Varioptic began its first shipment of the liquid lens in 2007 produced by Creative Sensor (Nanchang, China) but later partnered with Seiko Instruments (Chiba, Japan) for mass manufacturing. While Philips terminated its liquid lens project in 2011 (ref. 24) due to competition with a voice coil motor for camera phones and a small market for endoscopes, *etc.*, Varioptic chose diverse and niche markets including machine barcode readers,[31] intraoral cameras,[32] cell counters,[33] ophthalmology,[34] biometrics,[35] and low visions devices.[36] In recent years (since 2017), Verily Life Sciences, formerly Google Life Sciences and a subsidiary of Alphabet (Mountain View, USA), has filed multiple patents on electrowetting-based contact lens.[37,38] It is to be seen whether they will venture to commercial products.

Varioptic has gone through several changes and expansions in the 2010s, as schematically summarized in Fig. 5. In 2011, Varioptic was acquired by Parrot (Paris, France), a company well known for camera drones. At the same time, Optilux (Santa Barbara, USA) was founded with an exclusive right to use the liquid lens in smart phones and tablets. Then, as an interesting turn of events, Invenios (Santa Barbara, USA), a microfabrication foundry specializing in glass-based gene sequencing chips and microfluidic devices, acquired Optilux in 2013 and Varioptic from Parrot in 2016, only to be acquired immediately (in 2017) by Corning, a Fortune (Global) 500 Company specializing in glass and ceramics. Currently, the Varioptic liquid lenses are marketed as Corning Varioptic Lenses (Fig. 4(b)).

The reflective display

A droplet switched between beading and spreading on a hydrophobic surface, as illustrated in Fig. 2(a), can also be used as a switchable pixel for optical images, as illustrated in Fig. 6(a and b). Philips Research (Eindhoven, the Netherlands) filed an electrowetting display patent in 2002,[40] and its inventors Johan Feenstra and Robert Hayes founded a spinoff Liquavista (Eindhoven, the Netherlands) in 2006.

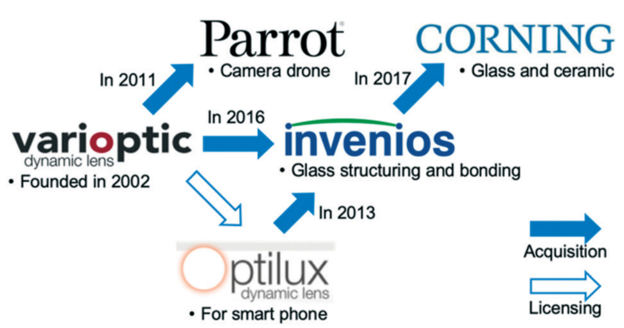

Fig. 5 History of the liquid lens business. Varioptic has been the world leader in liquid lens technology and the first example of successful commercialization for electrowetting. They are now Corning Varioptic Lenses.

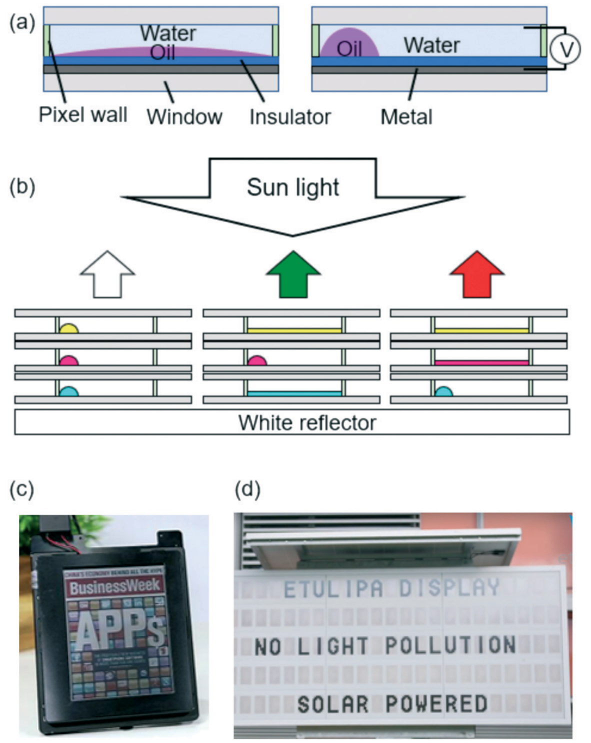

Fig. 6 Electrowetting-powered reflective display. (a) Working principle of a single cell of an electrowetting display. When voltage is applied, *e.g.*, 15 V, the dyed oil droplet is pushed away by wetting of the water. (b) Simplified working principle of an electrowetting colour reflective display, adapted from ref. 46 with permission from Etulipa. (c) A tablet with Liquavista's display.[47] (d) Etulipa's outdoor display powered by solar energy, adapted from ref. 48 with permission from Etulipa.

Compared with an electrophoretic display (E-ink), their electrowetting-powered display was fast enough to play video contents.[22] They moved forward to commercialize the display by improving its contrast, brightness, saturation, speed, power consumption, and reliability while achieving grayscale, full-color, and trans-reflective displays.

Liquavista was acquired by Samsung Electronics (Suwon, S. Korea) in 2010 and the technology matured.[41] However, Samsung changed their business strategy and Amazon (Seattle, U.S.A.) purchased the business in 2013 to develop color reflective video displays. We believe that they aimed to improve its e-reader, which is monochrome and has a slow refresh rate. Amazon was building a production team in Shenzhen, China as late as 2016,[42] but it shut down Liquavista at the end of 2018. Although the reason for the shutdown is not known, one can imagine a change of focus in the business strategy, technical challenges and fierce competitions, such as CLEARink with another video-speed reflective display technology.

The consumer market is not the only playing field for reflective displays. As Liquavista was being founded, Hans Feil founded Miortech (Eindhoven, the Netherlands) in 2006 as a spinoff of Liquavista and formed Etulipa (Eindhoven, the Netherlands) as a subsidiary of Miortech in 2013 to develop outdoor digital signage using electrowetting.

Compared with Liquavista's architecture which placed cell walls on the hydrophobic layer of the bottom glass,[43] Etulipa mounted the cell walls on the top glass and extended them to the bottom glass.[44] Reflective displays are attractive for outdoor signage not only because of their readability in bright light but also because they do not create light pollution. Because digital signs – much larger than electronic paper – require assembly of multiple tiles, Etulipa added an optical waveguide on top of the electrowetting display tiles to make them visibly seamless.[45] Unique challenges are to ensure superior reliability to withstand harsh outdoor conditions, such as flying particles, rain, temperature cycles, and sun radiation. While maturing the technology for a wide range of outdoor applications, their first application is an electronically changeable copy board (eCCB) named Carbon, boasting clear black digital lettering. The tiles that constitute the copy board are manufactured by United Radiant Technology (Taichung, Taiwan).

Fig. 7 schematically summarizes the history of the electrowetting-powered reflective display business to date. Recently, a team led by GuoFu Zhou and Alexander Henzen (former Philips employees who had earlier founded IRex Technologies, an electronic paper company spun off from Philips) has also been commercializing electrowetting displays in South China Normal University (China) and Shenzhen Guohua Optoelectronics (Shenzhen, China). It is still to be seen how the above three will overcome the challenges and bring attractive products to the market.

Digital microfluidics for biochemical assays

One can induce an aqueous droplet to slide on a hydrophobic surface by applying an electric potential between the droplet and the substrate only under one side of the droplet, as illustrated in Fig. 2(b). Since it implies that multiple droplets can be physically moved purely by electric signals, dramatically simpler microfluidic devices have become possible without calling for any physical pumps or valves, and a lab-on-a-chip could be envisioned, as illustrated in Fig. 8.

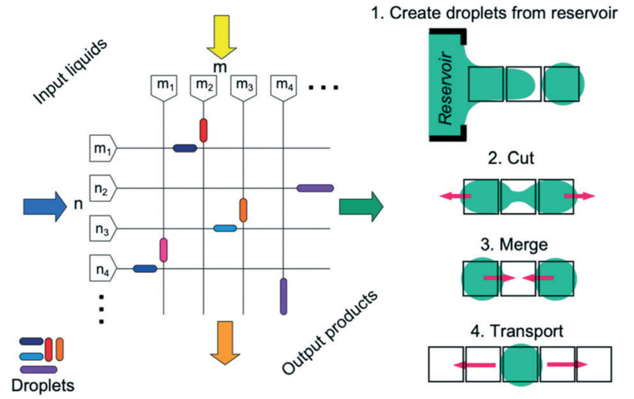

Fig. 8 Digital microfluidics and lab-on-a-chip application envisioned by manipulating a liquid by EWOD technology, adapted from ref. 2 and 17.

Alex Shenderov filed a patent for a device capable of manipulating droplets on a surface by EWOD actuation in 1999 (ref. 14) and founded Nanolytics (Raleigh, U.S.A.). Independently, UCLA (Los Angeles, U.S.A.) filed a similar patent in 2000,[15] and its inventor CJ Kim (the corresponding author of this paper) founded Core MicroSolutions (Los Angeles, U.S.A.) in 2002. Based on the collaborative research between Nanolytics and Richard Fair's lab in Duke University,[16] Michael Pollack and Vamsee Pamula founded Advanced Liquid Logic (Morrisville, U.S.A.) in 2004. All the three companies explored to commercialize EWOD digital microfluidics for a wide range of applications but mostly biomedical applications, such as accelerating the drug discovery process by replacing robotic manipulations of liquids with EWOD digital microfluidic manipulations. Eventually, Advanced Liquid Logic acquired Nanolytics in 2007 and Core MicroSolutions in 2009 before being acquired by Illumina (San Diego, U.S.A.) in 2013. Fig. 9 schematically summarizes the history of digital microfluidics companies based mostly on the PCB substrate.

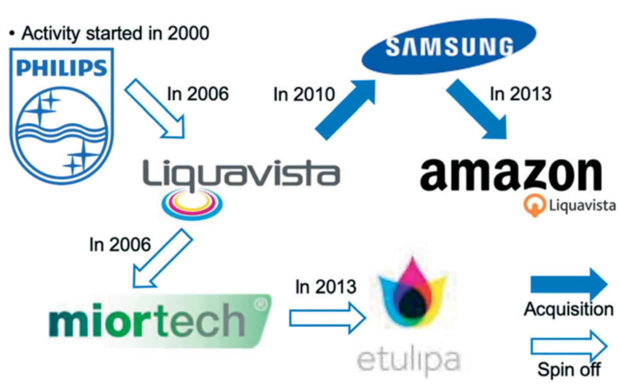

Fig. 7 History of the electrowetting-based reflective display business. Liquavista has pioneered electronic paper but encountered a recent setback. Currently, the utilities are expanding to outdoor applications.

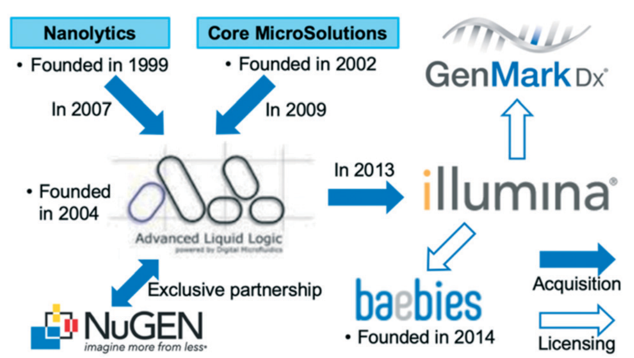

Fig. 9 History of the EWOD digital microfluidics business around Advanced Liquid Logic, which played a key role in two main products of today: GenMark's ePlex System for molecular diagnostics and Baebies' SEEKER for enzymatic assays for newborns.

Prior to the above acquisition, NuGEN Technologies (Redwood City, U.S.A, now part of Tecan Group in Männedorf, Switzerland) introduced a digital microfluidics-based DNA library preparation instrument called Mondrian SP Workstation[49] in 2011, in partnership with Advanced Liquid Logic. After the 2013 acquisition of Advanced Liquid Logic, Illumina launched a similar, expanded product called NeoPrep Library Prep System[50] in 2015, as shown in Fig. 10. Performing the majority of sample preparation steps automatically (*e.g.*, magnetic bead-based operations, thermal cycling, and optical detection) by EWOD, the system completed sample preparation in ∼30 min instead of the 4–5 hours of manual operation by users. Unfortunately, this system was discontinued in 2017 for undisclosed reasons, which are generally understood as reliability problems[51] likely caused by underestimating the challenges of engineering and manufacturing (the authors' opinion).

The setback of NeoPrep by Illumina did not discourage other sequencing companies from employing the EWOD digital microfluidics technology for similar goals. MGI, a subsidiary of BGI, launched DNBelab D series, a DNA sample preparation platform in 2019.[53] Oxford Nanopore Technologies (Oxford, United Kingdom) launched VolTRAX V2, as shown in Fig. 11, for DNA/RNA library preparation in 2018. Their consumables are the thin-film transistor (TFT)-based EWOD devices[54] supplied by Aqdrop (Oxford, United Kingdom). Compared with NeoPrep, VolTRAX V2 has several advantages for better reliability. First, its EWOD device is made of a glass substrate obtained using an LCD manufacturing method instead of the PCB substrate employed for NeoPrep's EWOD device. Compared with the PCB-based device, the glass-based EWOD device has a smoother (*i.e.*, less surface topography) surface, allowing a thinner dielectric layer and ensuring better control of the liquid volume. Second, feedback detection of liquid volumes is implemented in the system, allowing the users to dispense exact volumes of liquids into the device. Third, by reducing the number of libraries running at a time, their cartridge has a smaller chance to fail than NeoPrep's cartridge that runs 16 libraries in parallel. Although NeoPrep's cartridge was not large enough to run parallel experiments, it utilized methods such as DNA barcode to perform multiple sample processes.

Before the 2013 acquisition by Illumina, Advanced Liquid Logic was working with GenMark Diagnostics (Carlsbad, U.S.A.) to explore a fully integrated *in vitro* diagnostic platform that detects DNA/RNA targets using GenMark's eSensor®. GenMark obtained a license and continued the development to complete the ePlex System shown in Fig. 12, which is built to operate multiplex panels each for a certain disease diagnostics. Their ePlex System and the first panel (the respiratory pathogen or RP panel) were FDA cleared in 2017, and two other panels (the blood culture identification for Gram positive organisms or BCID-GP panel and the blood culture identification for fungal organisms or BCID FP panel) were FDA cleared in 2018, with additional panels in the pipeline. Currently, the GenMark ePlex system with its panels is considered to be the most sophisticated and versatile electrowetting product in the market.

In collaboration with the Neonatal-Perinatal Research Institute of Duke University, Advance Liquid Logic developed a molecular diagnostic system to detect lysosomal storage disorders (LSDs) for newborn babies. After the 2013 Illumina acquisition, Vamsee Pamula and Richard West obtained the license from Illumina and formed Baebies (Durham, U.S.A.) in 2014 to continue commercializing the LSD screening

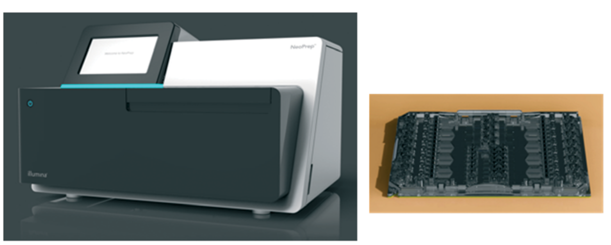

Fig. 10 Illumina's NeoPrep System and its consumable, adapted from ref. 52 with permission from J. Kurihara.

Fig. 11 Oxford Nanopore's automatic sample preparation on system for nanopore analyses, reproduced from ref. 55 with permission from Oxford Nanopore Technologies.

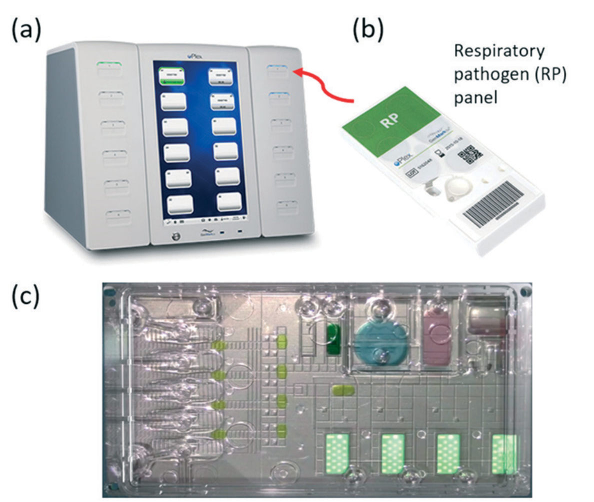

Fig. 12 GenMark Diagnostics' ePlex system and its consumable. (a) The system.[56] (b) The respiratory pathogen panel.[57] (c) Inside the panel, electrowetting is used to prepare samples for automatic molecular diagnostics.[57] The images are adapted with permission from GenMark Diagnostics.

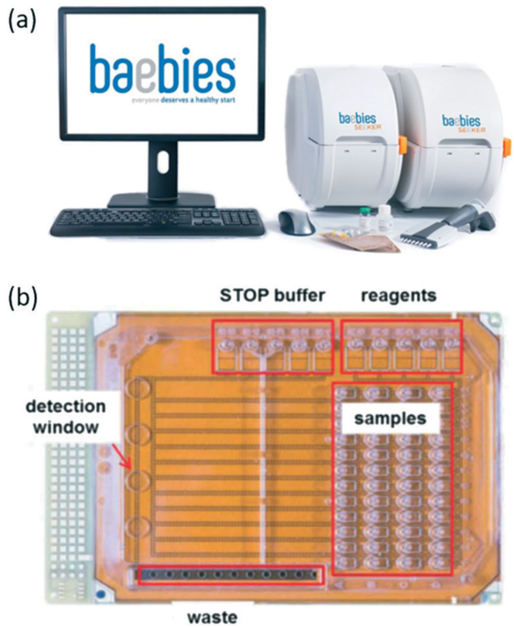

Fig. 13 Baebies' SEEKER. (a) The system.[58] (b) The consumable.[59] The images are adapted with permission from Baebies.

system and screening services for newborns. Their instrument SEEKER, shown in Fig. 13, was FDA approved in 2017.

Other companies and products

In recent years, more companies or products based on electrowetting started to emerge, mostly in biomedical applications. Spun off the University of Twente (Enschede, the Netherlands) in 2012, eMaldi[60] (Enschede, the Netherlands) provides more sensitive signals for matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS). Founded in 2012, Nicoya[61] (Kitchener, Canada) integrated digital microfluidics into a surface plasmon resonance (SPR) system to launch Alto in 2020.[62] Founded in 2012 as an electrowetting spinoff of the University of Toronto, Kapplex (Toronto, Canada) was acquired in 2016 (ref. 63) by the microRNA-detection company Miroculus (San Francisco, U.S.A.) to develop a sequencing library prep platform.[64] Unlike Illumina's NeoPrep System, their system does not use the filler oil.[65] Founded in 2016 and currently in an accelerator program hosted by Merck, Digi.Bio[66] (Amsterdam, the Netherlands) supplies their system and consumables to various companies, including Levels Diagnostics, as well as targeting own biochemical applications. A joint venture formed in 2017 by Sharp (Sakai, Japan) and Hon Hai Precision Industry (a.k.a. Foxconn) (Taipei, Taiwan), Aqdrop[67] (Oxford, United Kingdom) allows one to manipulate hundreds of droplets in one chip. They are not only currently supplying the TFT film-based EWOD devices to Oxford Nanopore Technologies but also exploring a wide range of biochemical applications in genomics, proteomics, cellomics, and synthetic biology. Founded in 2018, Digifluidic Biotech[68] (Zhuhai, China) integrates DNA melting curve analysis with digital microfluidics for fast nucleotide detection. Digifluidic Biotech and GenMark Diagnostics are currently working on a coronavirus detection kit.[69,70] Lastly, it is worth noting some recent initiatives to lower the initial barrier to electrowetting technology,[71–73] motivated by recognizing that the burden of engineering and manufacturing too often discourages individuals and labs, who may otherwise explore electrowetting for own ideas and applications.[73]

Conclusions

This review has summarized the history and status of the major commercialization activities of electrowetting technologies, covering liquid lenses, electronic displays, and various biochemical applications. The big picture reveals a few trends and teaches some good lessons. First, almost every electrowetting company worked on unique applications quite different from others even though the underlying technologies are similar. As different companies are focusing on different applications and pursuing different markets, the competition is still relatively mild. The efforts to address the reliability problems from the early days led to the breakthroughs for today's optical products. Second, while some of the ambitious products have experienced setbacks (Liquavista's electronic paper and Illumina's DNA/RNA library preparation system), they did not discourage others from continuing to pursue similar goals. Instead, others learned valuable lessons and adjusted their strategies to improve the product reliability or shift the target market. Third, the success of Advanced Liquid Logic suggests that collaborating with mature biochemical companies is important to explore biochemical applications – easy to say than do in practice. Fourth, now approximately 20 years after the first electrowetting company was founded and with most of the fundamental patents expired or approaching expirations, we start to see a surge of start-up companies formed and being formed and new products being developed and launched, as new applications continue to be discovered. Understanding the practical limitations of EWOD devices better and also learning how to design and manufacture more reliable EWOD products, the chances of success have been increasing for new companies and new products, allowing them to harvest from the wide potential of electrowetting and EWOD technologies.

Conflicts of interest

C.-J. K. is an inventor of multiple UCLA patents licensed to Illumina and being financially benefitted.

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